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Original Research

Treatment-related mortality in children with cancer: Prevalence and risk factors

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Abstract ***Aim:*** Intensive treatment regimens have contributed to a marked increase in childhood cancer survival rates. Death due to treatment-related adverse effects becomes an increasingly important area to further improve overall survival. In this study, we examined 5-year survival in children with cancer to identify risk factors for treatment-related mortality (TRM).
Methods: All children (aged <18 years at diagnosis) diagnosed with cancer in 2 Dutch university hospitals between 2003 and 2013 were included, survival status was determined and causes of death were analysed. Various demographic and treatment factors were evaluated, for which a multivariable competing risks analysis was performed.
Results: A total of 1764 patients were included; overall 5-year survival was 78.6%. Of all 378 deaths, 81 (21.4%) were treatment-related, with infection being responsible for more than half of these deaths. Forty percent of TRM occurred in the first three months after initial diagnosis. Factors associated with TRM in the multivariable competing risks analysis were diagnosis of a haematological malignancy, age at diagnosis <1 year and receipt of allogeneic haematopoietic stem cell transplantation. In children suffering from haematological malignancies, TRM accounted for 56.3% of 103 deaths.

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Conclusion: Over one in five deaths in children with cancer death was related to treatment, mostly due to infection. In children suffering from a haematological malignancy, more children died due to their treatment than due to progression of their disease. To further increase overall survival, clinical and research focus should be placed on lowering TRM rates without compromising anti-tumour efficacy. The findings presented in this study might help identifying areas for improvement.

1. Introduction

Cure rates of children with cancer have increased greatly in the past decades, largely because of more intensive, multimodal treatment regimens [1]. These treatment regimens are however associated with several adverse effects, such as pain, febrile neutropenia and nausea. These diminish quality of life and can have serious treatment implications, such as delay or reduction of anti-cancer treatment. In addition, some children with cancer die as a result of these intensive treatments. As the cure rates keep improving and fewer children die of cancer, treatment-related mortality (TRM) becomes an increasingly important area to further improve overall survival [2].

Various specific causes for TRM exist. A well-known cause is infection, which is the cause of death in one in 40 children with acute lymphoblastic leukaemia (ALL) [3]. The list of other causes of TRM is long, with haemorrhage, graft-versus-host disease and encephalopathy, amongst others [4]. Discriminating TRM and progressive disease (PD) death is not always straightforward. One might say all deaths are due to cancer as the child would not have undergone cancer treatment without the disease. It is also dependent on the specific type of cancer and accompanying intensity of treatment. In addition, there are causes that fit neither TRM nor PD death, for instance, an accident or death due to underlying comorbidity.

In 2015, the International Pediatric Oncology Mortality Classification Group (IPOMCG) acknowledged this complexity and introduced a consensus-based definition of TRM: death occurring in the absence of progressive cancer [5,6]. In addition, cause-of-death attribution system was introduced, validated and subsequently used in two Canadian studies focussing on differences between TRM and PD death and univariable risk factors for TRM [7–9].

In this study, we aimed to examine causes of death in a Dutch cohort of children with cancer, in five-year follow-up as well as in the first three months after diagnosis. We also aimed to explore known and novel risk factors for TRM in a multivariable manner and describe specific causes of TRM.

2. Methods

All children (aged <18 years at diagnosis) diagnosed with cancer between January 1st 2003 and December 31st 2012, and primarily treated at the University Medical Center Groningen (UMCG) and the Academic Medical Center (AMC) Amsterdam were eligible for inclusion.

2.1. Causes of death

TRM was defined in accordance with the aforementioned IPOMCG definition: death occurring in the absence of progressive cancer [6]. For all deceased patients, using the IPOMCG system, we attributed TRM or PD death and a probable or possible cause of TRM. In addition, we assigned the relevant ICD-10 (International Statistical Classification of Diseases) codes for cause of death [10].

2.2. Risk factors

Several factors, such as sex, diagnosis, age at diagnosis, nutritional status at diagnosis (using [BMI] z-scores, with “The Netherlands 2010, BMI for age” serving as reference), Intensity of Treatment Rating Scale 3.0 (ITR 3.0; reliable and valid classification to determine treatment intensity of paediatric oncology treatment protocols), haematopoietic stem cell transplantation (HSCT) including type, relapse, treatment era, were evaluated to determine their potential association with TRM and finally to investigate potential influence of delay and travel time to the nearest shared care hospital (UMCG only; using Google Maps with traffic deactivated) [11].

2.3. Data collection

Local data managers provided lists with eligible patients and relevant outcomes from the local childhood cancer registries. The individual electronic patient records were hand searched for missing and additional data (e.g. length and weight at diagnosis). In March 2018, for all patients, the survival status was verified in the Dutch population register to check correctness of our critical outcome (survival status).

Data regarding cause of death was extracted from the electronic patient records using a data extraction form that underwent a two-phase pilot. The first pilot focused on usability and consistency and included 20 randomly selected patients for which two researchers (J.B. and E.A.H.L.) independently extracted data. Inter-rater reliability (IRR) had to be >90%, or the pilot was repeated. The second pilot served to evaluate if the extracted data were sufficient to unambiguously determine TRM or PD death and main cause of TRM. In each centre, 20 patients were randomly selected and the data extraction form was completed by one researcher (J.B.), and subsequently two independent raters (J.B., R.R.G.K./E.A.H.L.) designated the cause of death using this form. The form was finalised when the IRR for cause of death was ≥95%.

Further data extraction was performed by one researcher (J.B.). After data extraction was completed, two independent researchers (R.R.G.K. and E.A.H.L.) classified the cause of death of all patients based on the information in the data extraction form. These results were compared, and all discrepancies were discussed in detail and resolved by consensus (or a third reviewer, W.J.E.T.).

2.4. Statistical analysis

Survival was defined as time from diagnosis till death; patients who were still alive five years after diagnosis were censored. As TRM and PD death are competing riskss (i.e. when one has occurred, the other cannot occur anymore), a competing risks analysis was necessary. The Fine and Gray proportional hazards model was used for these analyses, yielding subhazard ratios (SHRs) and 95% confidence intervals (CIs) [12]. These analyses were performed univariable and multivariable; in the latter, only variables with a significant association with TRM in univariable analysis were included. As the ITR 3.0 determination includes factors such as diagnosis, relapse and HSCT, the ITR 3.0 was separately multivariably analysed without these aforementioned variables. For categorical variables, the group in which the TRM was expected to be the lowest was chosen as the reference group. Cumulative incidence functions (CIFs) were plotted to visualise findings.

The significance level of all tests was determined at $p < .05$ and tested two-sided. Statistical analyses were performed using Stata Statistical Software: R15 (StataCorp LLC, College Station, TX, USA) and R v3.5.0 (R Foundation for Statistical Computing, Vienna, Austria) [13].

2.5. Sensitivity analysis

In case of missing data concerning cause of death, we planned to perform two-sided extreme scenario testing.

Table 1
Patient characteristics.

Variable	Total (n = 1764)		Haematological (n = 659)		Solid (n = 717)		Brain (n = 388)	
	n	%	n	%	n	%	n	%
Sex								
Female	792	*44.9*	275	*41.7*	332	*46.3*	185	*47.7*
Male	972	*55.1*	384	*58.3*	385	*53.7*	203	*52.3*
Age at diagnosis (years), median (interquartile range)	7.1 (3.1–12.6)	7.7 (3.7–13.0)	6.2 (2.0–12.6)	7.5 (3.8–11.8)				
Age at diagnosis (categories)								
Below 1 year	156	*8.8*	28	*4.2*	103	*14.4*	25	*6.4*
1–5 years	523	*29.6*	205	*3.1*	213	*29.7*	105	*27.1*
5–12 years	588	*33.3*	225	*34.1*	199	*27.8*	164	*42.3*
12–18 years	497	*28.2*	201	*30.5*	202	*28.2*	94	*24.2*
BMI z-score at diagnosis								
Between −2 and 2	1051	*84.7*	488	*86.4*	422	*86.1*	141	*75.8*
Below −2	96	*7.7*	36	*6.4*	36	*7.3*	24	*12.9*
Above 2	94	*7.6*	41	*7.3*	32	*6.5*	21	*11.3*
Relapse								
Yes	334	*18.9*	84	*12.9*	137	*18.9*	113	*29.1*
No	1430	*81.1*	569	*87.1*	586	*81.1*	275	*70.9*
HSCT								
Allogeneic	105	*6.0*	101	*15.5*	4	*.6*	0	*.0*
Autologous	108	*6.1*	18	*2.8*	66	*9.1*	24	*6.2*
No	1551	*87.9*	534	*81.8*	653	*90.3*	364	*93.8*
Deceased								
Yes	378	*21.4*	103	*15.6*	154	*21.5*	121	*31.2*
No	1386	*78.6*	556	*84.4*	563	*78.5*	267	*68.8*
Classification of cause of death								
PD	286	*16.2*	41	*6.2*	134	*18.7*	111	*28.6*
TRM	81	*4.6*	58	*8.8*	15	*2.1*	8	*2.1*
Unknown/unclassifiable	11	*.6*	4	*.6*	5	*.7*	2	*.5*

BMI, body mass index; HSCT, haematopoietic stem cell transplantation; PD, progressive disease; TRM, treatment-related mortality. Percentages are stated in italics.

This comprised re-running all analyses twice, first with the cases with an unknown cause of death assigned as TRM and second with these cases assigned as PD death. Results were compared with the original findings. If other variables had missing data, we ran the analyses again with the missing data imputed using multiple imputation (number of imputations dependent upon percentage of missing data according to Graham *et al.* with the lowest threshold [<1%] for tolerated power falloff) [14].

2.6. Ethical approval

This study was approved by the Medical Ethical Committee of the UMCG. Seeking informed consent was deemed not obligatory because of the nature of this study.

3. Results

3.1. Patient characteristics

A total of 1764 children diagnosed with cancer were included, with the median age of 7.1 years (interquartile range: 3.1–12.6 years). In total, 378 children (21.4%) died within five years of diagnosis, with a median survival of 364 days (interquartile range: 171–642 days). All patient characteristics are shown in Table 1.

3.2. Causes of death

For both phases of the extraction pilot, one round was sufficient to reach the IRR cut-off (see Supplemental Material S1 for final data extraction form). Three in every four deaths were due to PD (n = 286, 75.7%). TRM was the cause of death in 81 children (21.4%), corresponding to a 5-year cumulative incidence of TRM of 4.59% (95% CI: 3.62%–5.57%). In 11 children (2.9%), cause of death was either unknown (n = 10, no information in patient record) or not classifiable (n = 1, cause fit neither category).

Within diagnosis groups, the distribution of causes of deaths differed (Fig. 1). In children with a haematological malignancy, TRM was the major cause of death, with 58 of 103 deaths (56.3%) due to TRM and 41 (39.8%) due to PD. This was apparent particularly in children diagnosed with lymphoid leukaemia (n = 329), as 29 children (8.8%) died of TRM and 13 died of PD (4.0%). See also Supplementary Material S2.

Infection accounted for half of TRM (n = 43, 53.1%). A large proportion of TRM occurred in the first three months after initial diagnosis (n = 32, 39.5% of TRM), of which nearly half (n = 15, 46.9%) was due to infection. In fact, a subgroup analysis including only patients who did not relapse and did not receive an HSCT showed that nearly two of three (65.2%) deaths

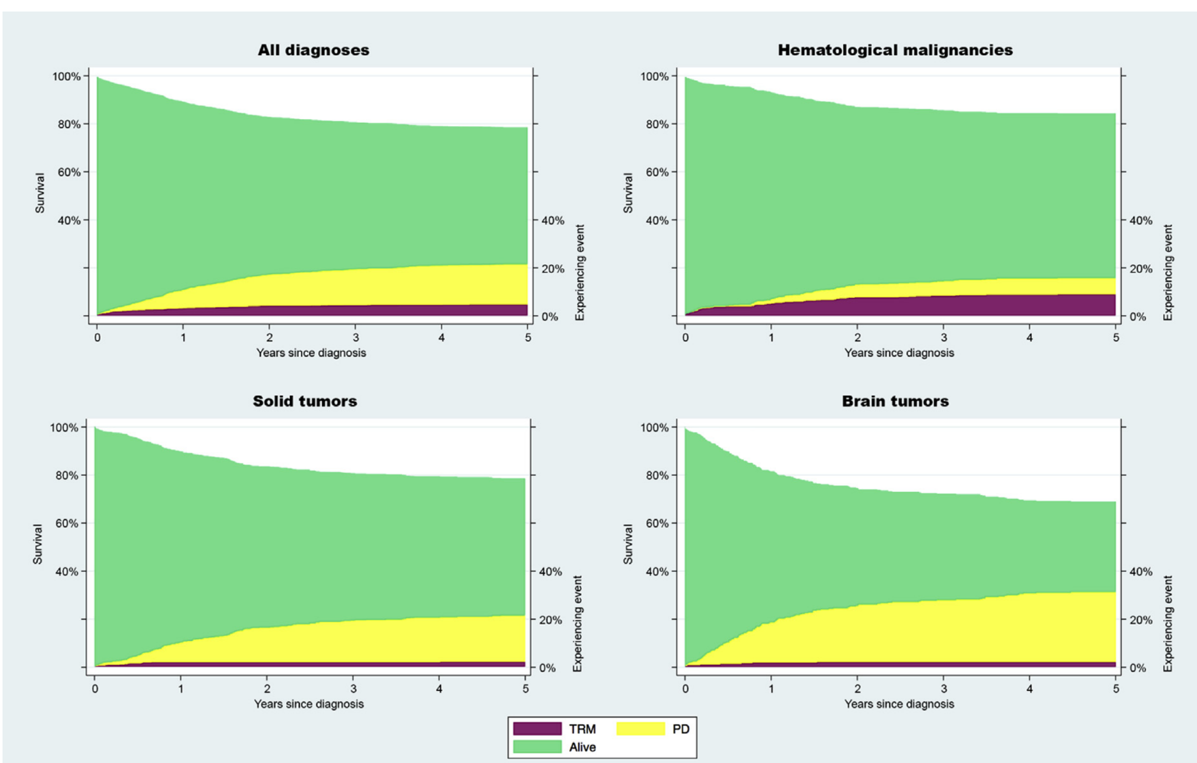


Fig. 1. Five-year survival status curves, displaying occurrence of treatment-related mortality (TRM) and death due to progressive disease (PD) within all diagnoses combined, children with a hematological malignancy, children with a solid tumour and children with a brain tumour.

due to infection occurred in the first three months after initial diagnosis. The vast majority (n = 13, 86.7%) of these early infection deaths occurred in children with a haematological malignancy (Table 2), with the associated pathogen being bacteria in six cases and *Candida* or *Aspergillus* in seven cases. See Supplementary Material S3 for ICD-10 codes.

3.3. Competitive risk analysis

In univariable competitive risk analyses, variables significantly associated with occurrence of TRM were diagnosis, age at diagnosis, ITR 3.0 and HSCT status (Table 3; for CIFs, see Fig. 2). In a subsequent multivariable analysis including these variables but the ITR 3.0, the following factors remained significantly associated with TRM: diagnosis of haematological malignancy (SHR: 4.29, 95% CI: 2.35–7.85, $p < .001$), age at diagnosis <1 year (SHR: 4.30, 95% CI: 2.09–8.87, $p < .001$) and use of allogeneic HSCT (SHR: 2.58, 95% CI: 1.51–4.43, p = .001). See Fig. 3 for a graphical representation of the analysis.

Looking at these groups in more detail (Supplementary Material S3), in patients with an allogeneic HSCT (n = 109), the majority of TRM cases (n = 19) died due to immunomediated causes (n = 8, 42.1%) or infection (n = 7, 36.8%). In patients younger than one year, TRM rates were especially high in those diagnosed with leukaemia (n = 24), with five cases of TRM (20.8%, two infection, one haemorrhage, one immunomediated, one central nervous system–related) and one case of PD death (4.2%).

In a separate extra multivariable analysis including the ITR 3.0 and age at diagnosis, the following factors were significantly associated with TRM: ITR 3.0 – level 4 (SHR: 2.13, 95% CI: 1.28–3.53, $p = .004$), ITR 3.0 – no treatment received (SHR: 3.20, 95% CI: 1.29–8.51, $p = .020$), age at diagnosis <1 year (SHR: 2.80, 95% CI: 1.38–5.69, $p = .004$) and age at diagnosis 12–18 years (SHR: 1.83, 95% CI: 1.01–3.30, $p = .046$).

3.4. Sensitivity analysis

Overall, there were very little missing data. Cause of death was, as stated, unknown in ten cases (2.6% of all deaths). As anticipated, the portion of missing data for BMI z-score at diagnosis (n = 523, 29.6%) was relatively high. Therefore, multiple imputations was

Table 2
Causes of treatment-related mortality, attributed according to the classification system by Alexander *et al.* [6].

Cause of TRM	Total (n = 1764)		Haematological (n = 659)		Solid (n = 717)		Brain (n = 388)	
	n	%	n	%	n	%	n	%
Total number of TRM cases								
During complete follow-up	81	*100*	58	*100*	15	*100*	8	*100*
In first 3 months	32	*39.5*	22	*37.9*	6	*40.0*	4	*50.0*
Infection								
During complete follow-up	43	*53.1*	30	*51.7*	6	*40.0*	2	*25.0*
In first 3 months	15	*18.5*	13	*22.4*	1	*6.7*	1	*12.5*
Haemorrhage								
During complete follow-up	6	*7.4*	5	*8.6*	1	*6.7*	0	*0.0*
In first 3 months	4	*4.9*	3	*5.2*	1	*6.7*	0	*0.0*
Cardiac system								
During complete follow-up	3	*3.7*	2	*3.4*	1	*6.7*	0	*0.0*
In first 3 months	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Immunomediated								
During complete follow-up	8	*11.1*	8	*13.8*	0	*0.0*	0	*0.0*
In first 3 months	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
CNS-related								
During complete follow-up	15	*17.3*	6	*10.3*	3	*20.0*	6	*75.0*
In first 3 months	9	*11.1*	4	*6.9*	2	*13.3*	3	*37.5*
Respiratory system								
During complete follow-up	5	*9.9*	4	*6.9*	1	*6.7*	0	*0.0*
In first 3 months	2	*2.5*	1	*1.7*	1	*6.7*	0	*0.0*
Gastrointestinal system								
During complete follow-up	1	*1.2*	1	*1.7*	0	*0.0*	0	*0.0*
In first 3 months	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
External causes								
During complete follow-up	2	*2.5*	0	*0.0*	2	*13.3*	0	*0.0*
In first 3 months	0	*0.0*	0	*0.0*	0	*0.0*	0	*0.0*
Classification not possible								
During complete follow-up	3	*3.7*	2	*3.4*	1	*6.7*	0	*0.0*
In first 3 months	2	*2.5*	1	*1.7*	1	*6.7*	0	*0.0*

Numbers are presented for the complete follow-up period (first five years after initial diagnosis) and for the first 3 months after initial diagnosis. TRM, treatment-related mortality; CNS, central nervous system. Percentages are stated in italics.

Table 3
Results of univariable and multivariable competing risks regression analyses (Fine and Gray proportional subhazards model).

Univariable	Survival status (5 years after initial diagnosis)								
	Alive (n = 1386)		TRM (n = 81)[a]		PD (n = 286)[a]		SHR[c]	95% CI[c]	*p*[c]
	n	%	n	%	n	%			
Sex									
Female	634	80.3	39	4.9	117	14.8	1		
Male	752	78.1	42	4.4	169	17.5	0.88	0.57–1.35	0.547
Diagnosis									
Solid tumour	563	79.1	15	2.1	134	18.8	1		
Haematological tumour	556	84.9	58	8.9	41	6.3	4.33	2.45–7.64	*<.001*
Brain tumour	267	69.2	8	2.1	111	28.8	0.99	0.42–2.33	0.976
Age at diagnosis									
< 1 yrs	116	74.4	13	8.3	27	17.3	2.83	1.38–5.79	*.004*
1–5 yrs	412	79.4	22	4.2	85	16.4	1.39	0.75–2.59	0.301
5–12 yrs	473	80.7	18	3.1	95	16.2	1		
12–18 yrs	385	78.3	28	5.7	79	16.1	1.86	1.03–3.37	*.039*
Intensity of Treatment Rating 3									
Level 1 & 2[b]	745	92.4	33	4.1	28	3.5	1		
Level 3	366	80.6	15	3.3	73	16.1	0.96	0.51–1.80	0.895
Level 4	245	54.6	33	7.3	171	38.1	2.10	1.27–3.48	*.004*
No treatment received	30	68.2	5	11.4	9	20.5	3.60	1.34–9.67	*.011*
HSCT									
No	1267	81.7	58	3.7	219	14.1	1		
Yes, allogeneic	65	61.9	19	18.1	18	17.1	4.93	2.99–8.14	*<.001*
Yes, autologous	54	50.0	4	3.7	49	45.4	0.99	0.36–2.72	0.978
Relapse									
No	1253	87.6	61	4.3	110	7.7	1		
Yes	133	39.8	20	6.0	176	52.7	1.39	0.84–2.28	0.200
BMI z-score at diagnosis									
−2.0 to 2.0	875	62.8	41	2.9	478	34.3	1		
< −2.0	63	64.3	5	5.1	30	30.6	1.37	0.54–3.47	0.501
> 2.0	35	81.4	3	7.0	5	11.6	1.92	0.59–6.28	0.279
Treatment era									
Jan 2003–Dec 2007	652	79.9	42	5.1	122	15.0	1		
Jan 2008–Dec 2012	734	78.3	39	4.2	164	17.5	0.81	0.52–1.25	0.335
Travel time shared care hospital									
<15 min	139	69.2	18	9.0	44	21.9	1		
≥15 min	455	80.8	27	4.8	81	14.4	0.67	0.37–1.22	0.186
Multivariable model 1	n	%	n	%	n	%	SHR[d]	95% CI[d]	*p*[d]
Diagnosis									
Solid tumour	563	79.1	15	2.1	134	18.8	1		
Haematological tumour	556	84.9	58	8.9	41	6.3	4.29	2.35–7.85	*<.001*
Brain tumour	267	69.2	8	2.1	111	28.8	1.20	0.50–2.88	0.68
Age at diagnosis									
< 1 yrs	116	74.4	13	8.3	27	17.3	4.30	2.09–8.87	*<.001*
1–5 yrs	412	79.4	22	4.2	85	16.4	1.47	0.79–2.74	0.228
5–12 yrs	473	80.7	18	3.1	95	16.2	1		
12–18 yrs	385	78.3	28	5.7	79	16.1	1.80	1.00–3.22	0.049
HSCT									
No	1267	81.7	58	3.7	219	14.1	1		
Yes, allogeneic	65	61.9	19	18.1	18	17.1	2.58	1.51–4.43	*.001*
Yes, autologous	54	50.0	4	3.7	49	45.4	1.39	0.51–3.80	0.523
Multivariable model 2	n	%	n	%	n	%	SHR[d]	95% CI[d]	*p*[d]
Intensity of Treatment Rating 3									
Level 1 & 2[b]	745	92.4	33	4.1	28	3.5	1		
Level 3	366	80.6	15	3.3	73	16.1	0.95	0.51–1.79	0.883
Level 4	245	54.6	33	7.3	171	38.1	2.13	1.28–3.53	*.004*
No treatment received	30	68.2	5	11.4	9	20.5	3.20	1.29–8.51	*.020*

Age at diagnosis									
< 1 yrs	116	74.4	13	8.3	27	17.3	2.80	1.38–5.69	*.004*
1–5 yrs	412	79.4	22	4.2	85	16.4	1.39	0.75–2.59	0.294
5–12 yrs	473	80.7	18	3.1	95	16.2	1		
12–18 yrs	385	78.3	28	5.7	79	16.1	1.83	1.01–3.30	*.046*

[a] 11 patients who died were either classified as unknown (n = 10) or not classifiable (n = 1).
[b] Level 1 and level 2 combined for statistical purposes (too few events in level 1 alone).
[c] Univariable competing risks regression analyses (Fine and Gray proportional subhazards model).
[d] Multivariable competing risks regression analyses (Fine and Gray proportional subhazards model) including diagnosis, age at diagnosis and HSCT.
TRM, treatment-related mortality; PD, progressive disease; HSCT, haematopoietic stem cell transplantation. Significant p-values are stated in italics.

performed using 20 imputations [14]. In all sensitivity analyses (two-sided extreme scenario testing and imputed data analysis), the same factors as in the original analyses were significantly associated with occurrence of TRM.

4. Discussion

This is the first study to combine the validated IPOMCG definition for TRM with a multivariable competing risks model to explore risk factors for TRM in a heterogeneous childhood cancer population. In our cohort of 1764 children with cancer, overall five-year survival was 78.6%. Over one in five deaths (21.4%) were treatment-related, and thus, one in every 22 children treated for cancer died due to their treatment within 5 years of diagnosis.

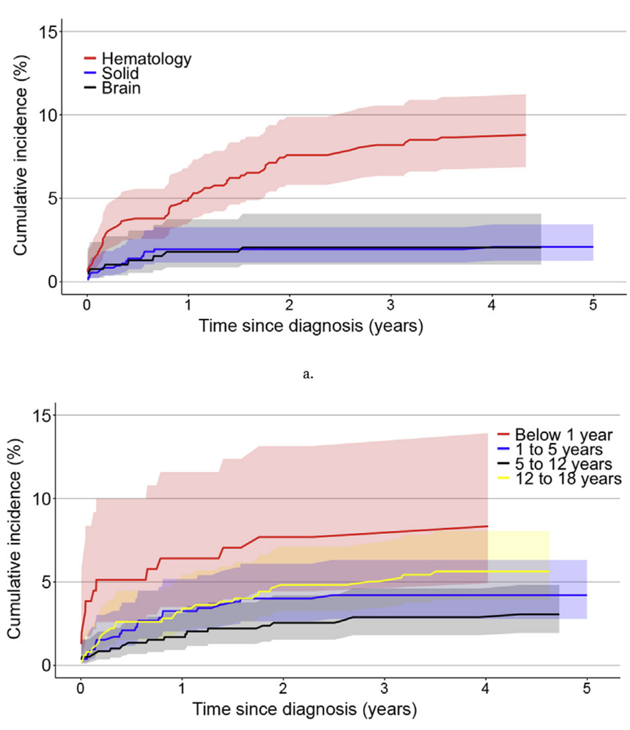
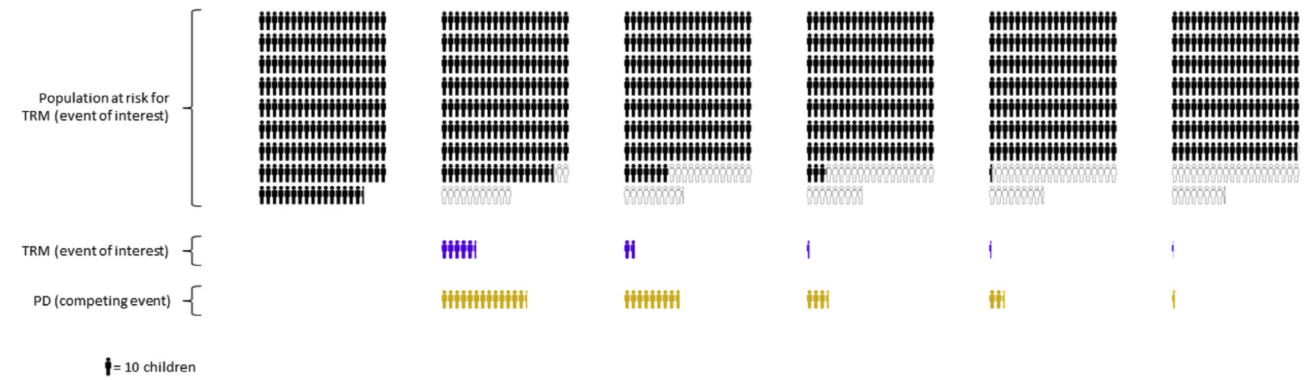


Fig. 2. Cumulative incidence functions (CIF) of treatment-related mortality in the presence of competing risks (death due to progressive disease) stratified by (a) type of malignancy and (b) age at diagnosis.

In the present study, TRM accounted for the majority of deaths (56.3%) in children with a haematological malignancy. Being diagnosed with a haematological malignancy was one of the factors related to TRM in multivariable competing risks model, as well as age at diagnosis <1 year and receipt of allogeneic HSCT. Hypothesising on these associations, in haematological malignancies, it might be the often used combination of glucocorticoids (inhibits immune responses) and aggressive chemotherapy (can cause severe neutropenia) that make patients susceptible for infections and thus TRM [15]. In children aged <1 year, we found that especially those diagnosed with leukaemia were susceptible for TRM, which might be explained by the poorer prognosis and thus more aggressive treatment regimen these children have to undergo than older children [16]. For children who had received an allogeneic HSCT, the higher rates of TRM are likely explained by potentially severe direct consequences of either the transplant (i.e. graft-versus-host disease) or the intensive conditioning regimen (i.e. veno-occlusive disease).

Because our cohort consisted of patients from two of seven Dutch paediatric oncology hospitals, we compared the distribution of diagnoses of our cohort with that of the Dutch Childhood Oncology Group registry (nationwide, diagnosed between 2003 and 2012) [17]. Our cohort was relatively comparable, with an overrepresentation of solid malignancies (40.5% vs. 37.4%) and an underrepresentation of haematological malignancies (37.1% vs. 40.8%) (Supplementary Material S2). This difference in distribution might have contributed to the overall survival being slightly lower than in other cohorts from other high-income settings [1]. However, with the high rates of TRM in children diagnosed with a haematological malignancy and the underrepresentation of this diagnostic group in our cohort, this implicates that the overall rate of TRM in the Dutch childhood cancer population might even be higher than in our cohort.

Comparing our findings with other reports on childhood cancer, TRM is challenging because of the different definitions that are used for TRM.



Time	t0 At diagnosis	t1 1 year after diagnosis	t2 2 years after diagnosis	t3 3 years after diagnosis	t4 4 years after diagnosis	t5 5 years after diagnosis
Alive	1,764	1,574	1,463	1,424	1,396	1,386
TRM	0	54	72	76	79	81
PD	0	134	222	257	281	286

Fig. 3. Risk table depicting the Fine & Gray subdistribution hazards model. A single silhouette depicts 10 children. In a competitive risk analysis, people who have suffered the competing event (in this case, PD) remain in the risk set (white silhouettes). Black silhouettes depict children still alive, blue silhouettes depict children who have died due to TRM and yellow silhouettes depict children who have died due to PD. TRM, treatment-related mortality; PD, progressive disease.

Nevertheless, one study that focused specifically on infection-related mortality in children with ALL found this to be the predominant cause of TRM, as did we [3].

One other study also used the IPOMCG definition and explored risk factors for TRM in a Canadian heterogeneous childhood cancer population and found a similar 5-year cumulative incidence of TRM (3.9% vs. 4.6% in our study) [9]. Although that study provided important insights, multivariable analyses were lacking. Identified univariable risk factors for TRM were leukemia/lymphoma diagnosis, age <1 year, metastatic disease, diagnosis before 01-01-2008 (data collection also from 2003 to 2012), HSCT and relapse. Importantly, survival status in this study was checked for on 31-12-2012; thus, some patients would still be in treatment. In our study, we collected data after 31-12-2017, so all patients had a complete follow-up of at least five years. This difference might explain the contrasting findings with respect to the significance of ‘diagnosis before 01-01-2008’.

During this study, we identified an important limitation of the classification system as proposed by the IPOMCG. In this classification, cause of death is designated as PD or TRM. Although TRM has the word ‘treatment’ in it, children who die before cancer therapy initiation are also classified as TRM. This is more logical than it might seem, as TRM entails deaths that could be prevented by better supportive care, which might be the case in children who die before start of therapy due to, for example, infection or bleeding. However, children who die due to accidents or homicide (none in our cohort) are also classified as TRM, which we believe is questionable. In addition, there are children who die due to a medical condition unrelated to their cancer (e.g. hereditary kidney disease) and thus do not fit any of the categories. Finally, there might be children for whom it is known that they are deceased (from e.g. the population register), but for whom the cause of death is unknown. For the aforementioned cases, the addition of an ‘unknown/unclassifiable’ category would be valuable. Although probably rare, deaths classified as ‘unknown/unclassifiable’ could either be treated as an added competitive event in competing risks analyses or have their influence explored using two-sided extreme scenario testing, as done in this study.

More, preferably even larger and international, studies to evaluate causes of death and risk factors for TRM in children with cancer are needed. In these studies, data should be collected in a prospective, standardised (and ideally automated) manner using the electronic patient records, as this would both increase completeness and accuracy and decrease workload. In addition, it would be worthwhile to collect more detailed information about treatment and supportive care received, for example, prophylaxis for infections.

This study also has implications for clinical care, most notably the focus on early infectious complications in children with haematological malignancies. These findings, and the notion that with increasing cure rates, the portion of children that die due to TRM might continue to grow, further emphasise the importance of seeking the right balance between desirable and undesirable consequences of treatment.

5. Conclusion

With a complete follow-up for our critical outcome (survival status), the use of a clear definition of TRM, the detailed description of designated causes of death for TRM and the use of multivariable competing riskss analyses, this study provides a new insight into the occurrence and aetiology of TRM. Overall, TRM accounted for one in five deaths in the first five years after diagnosis, with 40% of TRM deaths occurring in the first three months after diagnosis. In children with a haematological malignancy, more children died due to TRM than due to PD. Infection was the major cause of TRM, both overall and in the first three months after diagnosis. Clinical and research effort should be focused on lowering TRM rates by improving supportive care and lowering treatment intensity without compromising efficacy.

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Contributors' statement

E.A.H.L., R.R.G.K., J.B., H.M.B., L.C.M.K. and W.J.E.T. designed the study. E.A.H.L., R.R.G.K., J.B. and W.J.E.T. collected study data. Data analysis and interpretation was performed by E.A.H.L., R.R.G.K., J.B., E.A.M.L.F., J.H.M.M., A.M.J.R., J.A.L., R.P., H.M.B., L.C.M.K. and W.J.E.T. Manuscript draft by E.A.H.L., R.R.G.K., L.C.M.K., and W.J.E.T.. J.B., E.A.M.L.F., J.H.M.M., A.M.J.R, J.A.L., R.P. and H.M.B. critically appraised the manuscript. All authors agreed with submission of the final version of the article.

Conflict of interest statement

The authors have no conflicts of interest relevant to this article to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.08.008.

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